

205. A method for treating a bacterial infection in a patient, the method comprising administering to the patient in need thereof a composition in solid dosage form comprising amoxicillin and potassium clavulanate, such that the amount of amoxicillin is about 2000mg and comprising a first release phase and a second release phase;

the first release phase comprising potassium clavulanate and a first portion of the amoxicillin;

the second release phase comprising a second portion of amoxicillin, which is a pharmaceutically acceptable soluble salt of amoxicillin, and at least one pharmaceutically acceptable organic acid which are admixed in intimate contact at a ratio of from 20:1 to 1:2 (amoxicillin free acid equivalent to organic acid equivalent); such that the weight ratio of amoxicillin to potassium clavulanate is from 2:1 to 20:1, and the solid dosage is administered at a regimen interval of about 12 hours,

and wherein the solid dosage is such that the amount of amoxicillin released over thirty minutes is in the range about 45 to about 65% of the total amoxicillin content, over sixty minutes is in the range about 50 to about 75% of the total amoxicillin content, over two hours is in the range about 55 % to about 85% of the total amoxicillin content, over 180 minutes is in the range about 70 % to 95% of the total amoxicillin content and over 240 minutes is in the range about 70 to about 100% of the total amoxicillin content, as tested by the USP Dissolution Test, Apparatus 2, method at 37 degrees C, a paddle speed of 75 rpm and in 900 ml deionized water, over a period of 8 hours;

chosen such that the mean maximum plasma concentration (C<sub>max</sub>) is at least 12 micrograms/ml and the mean time the plasma concentration exceeds 4 micrograms/ml is at least 4.4 hours, when tested in a group of at least 7 healthy humans, based on blood sampling at half hourly intervals for the first two hours and thereafter at hourly intervals, (at the start of a light meal and after an overnight fast).

#### REMARKS

Claims 14 to 17 have been cancelled. Claims 13 and 18 have been amended. Claims 69 to 205 have been added. Support for these amendments lie in the original claims as well as in the specification on, for example, page 4, lines 1 to 3, 6 to 3, and 27 to 29; page 5, lines 19 to 23; page 7, lines 18 to 32; page 8, lines 14 to 22 and 32 to 36; page 9, lines 10 to 3; page 11, lines 17 to 29; page 12, lines 1 to 8 and 26 to 32; page 13, lines 3 to 31; page 14, lines 3 to 35; page 15, lines 1 to 7 and 20 to 28; page 16, lines 1 to 2 and 20 to 33; page 17, lines 3 to 6 and 10 to 11; page 18, lines 19 to 35; page 19, lines 1 to 27 and 35 to 36; page 20, lines 1 to 4; page 24, lines 3 to 11; page 25, lines 11 to 16; page 26, lines 21 to 23, Examples 1 and 2, pages 29 to 30; page 41, lines 19 to 30;

Figure 2; and Figure 5. No new matter is believed added. Applicants reserve their right to file divisional or continuation applications on cancelled or deleted subject matter.

A fee calculation sheet accompanies this response.

Attached hereto is a marked-up version of the changes made to the claims and the specification by the current amendment. The attached page is captioned "Version with markings to show changes made".

Applicants thank Examiner Bennett and Examiner Kishore for so graciously permitting the interview in the above noted application held on 10 September 2002. It is believed that this response resolves any claim drafting issues raised during the interview.

### **Judicially Created Obviousness-Type Double Patenting**

Claims 13 to 16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1 to 4, 69-73, and 95 of co-pending application no. 09/544019. As both applications are still pending without notice of allowable subject matter, Applicants respectfully request that this rejection be held in abeyance until such time as the claims are found allowable.

Claims 13 to 18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 11 to 15 of U.S. Patent 6,294,199 ('199) in view of the Merck Index. Applicants respectfully traverse this rejection.

The claims in the '199 patent contain a particular amount of amoxicillin, 1400 to 1900mg, which produces a particular mean plasma level over a particular time frame along with a particular C<sub>max</sub>.

The claims as amended herein recite a first release phase and a second release phase. The first release phase comprises both amoxicillin and potassium clavulanate, and the second release phase comprises amoxicillin. The second release phase also comprises a pharmaceutically acceptable organic acid in a ratio of 20:1 to 1:2 (amoxicillin:organic acid). The claims are not limited to a particular dosage amount, nor to a particular mean plasma concentration or maximum plasma concentration.

Claims 11 to 15 of the '199 patent do not recite first and second release phases, potassium clavulanate, or a pharmaceutically acceptable organic acid. These attributes of the pending claims are not remedied by the secondary reference, The Merck Index, which is cited to disclose clavulanic acid in combination with amoxicillin. Thus, this combination of references cannot form the basis of obviousness-type double patenting.

In view of these remarks and amendments, reconsideration of the rejection to the claims under the judicially created doctrine of obviousness-type double patenting is respectfully requested.

### **Rejection under 35 USC § 112**

Claim 18 is rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Applicants respectfully traverse this rejection.

Claim 18 as originally filed recited treating "*S. pneumoniae* (including Drug Resistant and Penicillin Resistant *S. pneumoniae*)". This claim language was not intended to limit the grouping of organisms to less than the whole, but to expressly include a grouping which might otherwise be considered a subset outside the recitation of *S. pneumoniae*. However, as the method can be used for the treatment of *S. pneumoniae* which are not drug resistant or penicillin resistant as well as Drug Resistant and Penicillin Resistant *S. pneumoniae*, the amendment to the claim is not a limitation. In addition, claim 69 has been added to expressly include the subset of Drug Resistant and Penicillin Resistant *S. pneumoniae* from cancelled claim 18, thereby removing any basis for this rejection.

In view of these remarks and amendments, reconsideration of the rejection to the claim under 35 USC §112, second paragraph, is respectfully requested.

### **Rejection under 35 USC § 103**

Claims 13 to 18 are rejected under 35 USC §103(a) as being unpatentable over Burch (WO 97/09042 or hereinafter '042). Applicants respectfully traverse this rejection.

WO 97/09042 corresponds to published US Patent Application 20010043926, as co-pending application USSN 08/722,259. Also related is US Publication Application 20010038838 or USSN 09/788,948.

Burch '042 teaches the use of higher ratios of amoxicillin and clavulanate in immediate release formulations for infections potentially caused by Drug Resistant and Penicillin Resistant *S. pneumoniae*. The '042 application recognized that strains of various organisms, in particular *S. pneumoniae*, were evolving, and that patients were exhibiting decreasing susceptibility to  $\beta$ -lactams as well as to other antibiotics, leading to ineffective treatment. According to the '042 application, it was unexpectedly found that increasing the dosage of amoxicillin to 1750mg/day (from the commonly used 875mg/day) and dosing twice daily yielded an effective antibiotic regimen to treat empiric infections potentially caused by DRSP.

The present application also relates to a method of treating bacterial infections by administering amoxicillin and potassium clavulanate. Further, the composition may be used to treat infections caused by the organisms *S. pneumoniae* (including Drug Resistant and Penicillin Resistant *S. pneumoniae*), *H. influenzae* and/or *M. catarrhalis*.

Unlike Burch '042, however, the claimed method involves administration of a composition that is not an immediate release formulation. Rather, it is a modified release (MR) formulation that contains two release phases, a first release phase comprising both amoxicillin and potassium clavulanate, and a second release phase comprising amoxicillin. Although the first release phase is similar to that of an immediate release (IR) formulation, the second release phase is a modified release formulation, which together with the first phase, produces two "peaks" in the plasma profile of the formulation in *in vivo* studies. The Examiner's attention is directed to Figure 5, profiles A and B, for instance, which demonstrate this "bi-phasic" response (i.e., two humps on the curve from both phases of the formulation). This is in contrast to the traditional or "standard" curve shown in Figure 4 for Formula (V), which is an immediate release formulation.

The modified release characteristic of the compositions of these method claims derives from a component in the second release phase that is not taught or suggested by the Burch '042 application, a pharmaceutically acceptable organic acid. As set forth in the claims, the pharmaceutically acceptable organic acid is present in the formulation in a 20:1 to 1:2 ratio. Applicants have found that the combination of a pharmaceutically acceptable soluble salt of amoxicillin, and a pharmaceutically acceptable organic acid, unexpectedly results in a tablet with modified release properties for the amoxicillin component. The modified release is present even when a conventional release modifier, usually utilized to evince such an effect, is not present.

To understand this process, Applicants offer the following explanation, illustrated by the slow release layer of Example 1 of the specification, page 29. The preferred ratio of a pharmaceutically acceptable soluble salt of amoxicillin, such as sodium amoxicillin (SA), to an organic acid is dependent upon the available carboxylic functionalities of the acid. For instance, citric acid (CA) contains three acid moieties and can therefore be used in a 3:1 molar ratio, i.e., one carboxylic function of CA for each molecule of SA.

Specifically, the molecular weight of sodium amoxicillin is 387.4 g/mole, and the slow release layer of the formulation in Example 1 contains 480.8mg/tablet. Dividing the amount of amoxicillin in the tablet by its molecular weight yields the amount of millimoles/tablet:

$$480.8 / 387.4 = 1.24 \text{ millimoles (per tablet)}$$

Performing the same calculation for citric acid, wherein the molecular weight of citric acid is 192.1 g/mole and the formulation contains 78.0 mg/tablet, yields the following:

$$78.0 / 192.1 = 0.41 \text{ millimoles (per tablet)}$$

A comparison of these two components in millimoles results in:

1.24 millimoles of sodium amoxicillin/ 0.41 millimoles of citric acid = 3.0. Therefore, 3 mole (parts) of sodium amoxicillin are combined with 1 mole (part) of citric acid per tablet (3:1). In other words, the tablets contain a molar ratio of sodium amoxicillin to citric acid of 3:1. Significantly, this molar ratio will provide a complete acid-base neutralization since sodium amoxicillin is a monovalent base and citric acid is a trivalent acid. Accordingly, one can also use the terminology that each tablet contains a 1:1 molar equivalent of base to acid. A "molar equivalent" means that one mole of base is provided for each mole of acid. Here, it takes three moles of sodium amoxicillin to provide the equivalent of one mole of citric acid, since citric acid has three acidic protons.

The Burch '042 application does not teach nor suggest the combination of two release phases, nor does it teach or suggest an immediate release phase and a modified release phase. In addition, the '042 application does not teach nor suggest that their formulation would achieve a prolonged time above minimum inhibitory concentration or mean plasma concentration such as those claimed in claims 179 to 184 and 191 to 193 herein. Thus, the skilled artisan would not be motivated to use the disclosure of the Burch '042 application to develop the claimed method for treatment using a composition for modified release based on the claimed first and second release phases.

In view of these remarks and amendments, Applicants respectfully request reconsideration of the rejection to the claims under 35 USC §103.

The Examiner requested in the interview of September 10, 2002 that Applicants discuss effervescent coupling systems in their response to the outstanding office action. Therefore, please note the following.

An effervescent coupling system includes both an acidic coupling reagent and a basic coupling reagent, the basic component liberating carbon dioxide when it and the acidic component are exposed to an aqueous environment. Examples of commonly used acidic components include citric acid and acidic salts thereof, such as sodium hydrogen citrate. Examples of commonly basic components include alkali metal carbonate and bicarbonate salts such as sodium bicarbonate.

The use of effervescent systems with amoxicillin trihydrate, or ampicillin, is known in the art. *See*, for instance, US 5,670,170; US 6,051,254; US 5,814,337; US 6,077,536; and US 5,225,197. In each of these, amoxicillin is used as amoxicillin trihydrate, rather than as a soluble salt such as sodium amoxicillin.

In contrast, the modified release properties of the SA/CA combination are due to the micro-reaction of the two components into a "confined environment" in the presence of water. This is achieved by admixing (in intimate contact with each other) the two

components, citric acid and sodium amoxicillin (in solid form) within the solid matrix of the composition. As water starts to penetrate the solid matrix, sodium amoxicillin reacts with citric acid to form amoxicillin, which is then hydrated to form amoxicillin trihydrate. Amoxicillin trihydrate precipitates out of solution and forms a lattice network of needle-like crystals. This contributes to the hydrated tablet crust found upon *in vitro* dissolution testing. Amoxicillin trihydrate has much lower water solubility than sodium amoxicillin and thereby produces a slower release of active agent into the system. It is this, which is believed to provide the observed MR effect.

The Examiner has also asked for a discussion of buffering systems in the context of the invention claimed in the present application. A buffer comprises two components, such as a monohydrogen phosphate and a dihydrogenphosphate salt or a monohydrogen citrate and a dihydrogen citrate salt in equilibrium, and maintains the pH of a solution at a desired level by adjusting the equilibrium by, for instance, mopping up loose protons. The components of the buffer need to be in solution before they can become functional.

In the present invention, the organic acid for instance, citric acid, is in intimate contact with the salt of the amoxicillin, e.g., sodium amoxicillin, and reacts with it, as water starts to penetrate the solid matrix of the composition, in a one way reaction, to form amoxicillin which is then hydrated to form amoxicillin trihydrate which has limited solubility. Thus, the organic acid is not acting as a buffer in the present invention.

Buffer systems are not generally added to solid compositions of amoxicillin – clavulanate such as in tablet formulations. Patent applications directed to such inventions do not generally include mention of such in the general listing of excipients, alongside diluents, disintegrants, lubricants, glidants, flavouring agents, colorants, preservatives, and desiccants etc. See, for instance, US 6,051,255 (Conley), column 2, lines 9 to 27.

For compositions containing clavulanate in solution or suspension, Application WO 93/00898 (Clapham) teaches, at page 1, lines 8 to 22:

"Pharmaceutical formulations containing a  $\beta$ -lactam antibiotic and clavulanic acid or derivatives such as its salts are known. Clavulanic acid in aqueous suspension or solution is known to suffer to some extent from instability, and one significant determinant of stability is the pH of the aqueous medium of the suspension or solution, pH 5.8 - 6.2 being known to be the optimum."

At present, the pH of pharmaceutical formulations containing clavulanic acid in suspension or solution is modified by including succinic acid in the formulation. *Attempts have been made to further control the pH by the use of buffer salts, but it is found that many commonly used pharmaceutically acceptable buffer salts such as phosphate, citrate, carbonate etc have a catalytic effect deleterious to the stability of the clavulanic acid, and moreover the increased ionic strength of the suspension is also believed to be deleterious to clavulanic acid stability.* [Emphasis added.]

The use of succinic acid referred to in the above quotation notably occurs at a much lower level of acid to clavulanate. *See also* the amount disclosed in WO 96/34605 (Bax and Ramsey) which is 0.84 mg of succinic acid and 61.56 mg of clavulanic acid. Thus, it is generally not appropriate to add a buffer to a liquid amoxicillin – clavulanate composition because of the adverse effect it would have on clavulanate stability.

Applicants hope that the preceding discussion provides sufficient explanation of various points raised during the interview. The Examiner is urged to contact the undersigned if any additional information or copies of the cited application are requested.

#### CONCLUSION

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. It is not believed that this paper should cause any additional fees or charges to be required, other than expressly provided for already. However, if this is not the case the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



Dara L. Dinner  
Attorney for Applicants  
Registration No. 33,680

GLAXOSMITHKLINE  
Corporate Intellectual Property - UW2220  
P.O. Box 1539  
King of Prussia, PA 19406-0939  
Phone (610) 270-5017  
Facsimile (610) 270-5090  
revised21685.doc

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 14 to 17 have been cancelled.

Claims 69 to 205 have been added.

Claims 13 and 18 have been amended as follows:

13 (amended) A method for [of] treating a bacterial infection [in a human in need thereof, which method comprises] in a patient, the method comprising:

administering to [said human] the patient in need thereof a [dosage of a therapeutically effective amount of] therapeutically acceptable amount of a composition in solid form comprising amoxicillin and potassium clavulanate [such that the amount of amoxicillin is in the range 1400 to 1900 mg, and an amount of potassium clavulanate such that the weight ratio of amoxicillin to potassium clavulanate is from 2:1 to 14:1, at a dosage regimen interval of about 12 hours, such that the regimen provides a mean plasma concentration of amoxicillin of 4 µg/mL for at least 4.4 h, and a mean maximum plasma concentration (C<sub>max</sub>) of amoxicillin of at least 12 µg/mL.] and comprising a first release phase and a second release phase;

the first release phase comprising potassium clavulanate and a first portion of the amoxicillin;

the second release phase comprising a second portion of amoxicillin, which is a pharmaceutically acceptable soluble salt of amoxicillin, and at least one pharmaceutically acceptable organic acid which are admixed in intimate contact at a ratio of from 50:1 to 1:5 (amoxicillin free acid equivalent to organic acid equivalent).

18 (amended). A [The] method according to claim 1 in which the bacterial infection is caused by [the organism] at least one of the organisms *S. pneumoniae* [including Drug Resistant and Penicillin Resistant *S. pneumoniae*], *H. influenzae*, and [or] *M. catarrhalis*.